

## HERBS AND SPICES: UNEXPECTED SOURCES OF ANTIEPILEPTOGENIC DRUG TREATMENTS?

**Protective Effect of Resveratrol Against Kainate-Induced Temporal Lobe Epilepsy in Rats.** Wu Z, Xu Q, Zhang L, Kong D, Ma R, Wang L. *Neurochem Res* 2009;34(8):1393–1400. Resveratrol (Res) is a phytoalexin produced naturally by several plants, which has multifunctional effects such as neuroprotection, anti-inflammatory, and anti-cancer. The present study was to evaluate a possible anti-epileptic effect of Res against kainate-induced temporal lobe epilepsy (TLE) in rat. We performed behavior monitoring, intracranial electroencephalography (IEEG) recording, histological analysis, and Western blotting to evaluate the anti-epilepsy effect of Res in kainate-induced epileptic rats. Res decreased the frequency of spontaneous seizures and inhibited the epileptiform discharges. Moreover, Res could protect neurons against kainate-induced neuronal cell death in CA1 and CA3a regions and depressed mossy fiber sprouting, which are general histological characteristics both in TLE patients and animal models. Western blot revealed that the expression level of kainate receptors (KARs) in hippocampus was reduced in Res-administrated rats compared to that in epileptic ones. These results suggest that Res is a potent anti-epilepsy agent, which protects against epileptogenesis and progression of the kainate-induced TLE animal.

**Curcumin Protects Against Electrobehavioral Progression of Seizures in the Iron-Induced Experimental Model of Epileptogenesis.** Jyoti A, Sethi P, Sharma D. *Epilepsy Behav* 2009;14(2):300–308. The purpose of the study was to investigate whether dietary intake of curcumin can inhibit the onset and progression of seizures and their associated pathophysiology in experimental FeCl<sub>3</sub>-induced epileptogenesis. Curcumin was considered for this study because it can cross the blood–brain barrier and bind redox-active metal ions. It is also well known for its antioxidative, anticancer, and anti-inflammatory properties. In the present study, seizures were induced by intracortical injection of FeCl<sub>3</sub> into young rats. Synchronized video/EEG recordings were obtained to diagnose the progression of seizures. Short-term treatment with a curcumin-supplemented diet (1500 ppm w/w) significantly inhibited the onset of grade III and IV seizures in rats with iron-induced epilepsy. The lower dose of curcumin (500 ppm) was not effective in inhibiting grade III seizures, but retarded the onset and progression of generalized seizures. The seizure-suppressing potential of curcumin is explained by the observed biochemical, behavioral, and ultrastructural results. Our results indicate that curcumin significantly prevents generalization of electroclinical seizure activity as well as the pathogenesis associated with iron-induced epileptogenesis.

### COMMENTARY

The development of medications for epilepsy has always been a priority of epilepsy research. About a dozen new drugs have become available over the past 15 years, many of which were discovered through the highly successful NIH Anticonvulsant Screening Program. While the newer medications have helped control seizures and minimize side effects for numerous epilepsy patients, two significant limitations have been noted with most currently available antiepileptic drugs, both old and new. First, despite the addition of newer seizure medications, the number of medically refractory epilepsy patients continues to constitute about one-third of all people with epilepsy (1). Second, current medications primarily act to symptomati-

cally suppress seizures; however, there is minimal clinical evidence that they correct the underlying brain abnormalities causing epilepsy (epileptogenesis) or alter its natural history and long-term prognosis (2). Thus, a widely recognized goal of epilepsy drug research is the identification of disease-modifying or antiepileptogenic drugs that can inhibit the progression of epilepsy or completely prevent its development in the first place (3). However, at this point, no proven antiepileptogenic therapies have been developed for clinical use.

A key reason that antiepileptogenic therapies have not yet been established is that current seizure medications act primarily on molecular mechanisms that generate the end-stage symptoms of epilepsy, that is, the seizures themselves. Many antiepileptic medications were identified through screening assays that assessed efficacy against acutely provoked seizures in nonepileptic animals. As a result, they inhibit seizures through mechanisms that directly decrease neuronal excitability, such as by modulating neurotransmitter receptors and ion channels.

Since most of these drugs were not tested in chronic, preventative assays of epileptic animals, it is not unexpected that they may be less effective at modulating underlying mechanisms of epileptogenesis than at ameliorating seizures.

A better strategy for developing antiepileptogenic therapies might be to interrupt the initial mechanistic events that trigger downstream cellular and molecular changes in the brain that lead to seizures. This approach is particularly plausible and clinically relevant for acquired epilepsies that are caused by a remote brain injury (e.g., head trauma, stroke), with seizures starting after a prolonged period, from months to years later. During the latent period of epileptogenesis, histopathological and molecular changes (e.g., neuronal death, synaptic reorganization) that promote epileptogenesis occur and could be targeted for correction by an antiepileptogenic therapy.

The search for antiepileptogenic treatments might utilize a number of strategies. In the most rational, hypothesis-driven approach, drugs are developed to target a specific mechanism of action implicated in epileptogenesis. On the other extreme is a screening method, akin to the NIH Anticonvulsant Screening Program, in which potentially effective substances are randomly assessed, irrespective of the mechanism of action. An intermediate, pragmatic approach is to utilize compounds that have known or suspected biological properties or clinical efficacy for other conditions or diseases that intuitively would appear to have relevance for epilepsy, although the specific mechanism of action may not be known. In this respect, there has been recent interest in investigating compounds derived from plants and other natural products that may have medicinal applications. Although herbal therapy for epilepsy and other neurological disorders has a long tradition in some cultures, the mechanisms of action of most of these treatments have remained unknown, largely because research on this topic is rare (4). Recent studies, however, have begun to elucidate potential neuroprotective and antiepileptogenic actions of substances of botanical origin.

Resveratrol is a polyphenol chemical found in a number of plant species, including peanuts and grapes, but with significant amounts in red wine. In normal plant physiology, resveratrol is produced as a defensive response to injury or parasitic attacks. Resveratrol has diverse biological properties and actions with potential clinical applications, including antiinflammatory, antioxidant, antiproliferative, and neuroprotective effects. Based primarily on animal models and cell culture, there is some evidence that resveratrol could be a potential treatment for a variety of diseases, ranging from cancer, cardiac disease, and neurodegenerative disorders, such as Alzheimer's, Huntington's, and Parkinson's, although rigorous clinical data in people are sparse (5).

A number of biological properties of resveratrol suggest that it could also be beneficial for epilepsy, particularly as an antiepileptogenic treatment. Previous studies indicated that

resveratrol protects against neuronal death and acute seizures induced by the glutamate agonist, kainate (6,7). The recent study by Wu et al. examined the effect of resveratrol on epileptogenesis in the chronic kainate model, in which spontaneous seizures develop after a latent period following an episode of kainate-induced status epilepticus. Resveratrol treatment prevented the development of epilepsy in most rats and correspondingly decreased kainate-induced neuronal death, mossy fiber sprouting, and kainate receptor upregulation—all putative mechanisms of epileptogenesis, consistent with a strong antiepileptogenic action.

A very similar story has emerged for another polyphenol compound, curcumin, which originates from the *Curcuma longa* plant and is the principal ingredient in the popular Indian spice, turmeric. Turmeric has been used for centuries in parts of India as an herbal therapy for a variety of symptoms and medical conditions, ranging from infections and inflammatory diseases to cancer; however, it also is used to treat neurological diseases, such as Alzheimer's and epilepsy. Although, again, controlled clinical trials documenting efficacy are lacking, intense interest in curcumin as a potential therapeutic agent has stemmed from accumulating information on its diverse biological properties, including anti-inflammatory, antioxidant, and chemotherapeutic activity (8). Similar to resveratrol, curcumin has been shown to inhibit acute seizures and neuronal death in the kainate model (9). The recent study by Jvoti et al. investigated the effect of curcumin on epileptogenesis in a rat model of posttraumatic epilepsy, in which iron injections into the neocortex mimics neuronal injury that occurs with blood extravasation during traumatic brain injury. Curcumin treatment decreased the development and progression of EEG abnormalities and seizures following the iron injection as well as improved deficits in spatial learning.

These two studies suggest that both resveratrol and curcumin retard epileptogenesis and could be considered potential antiepileptogenic therapies for epilepsies caused by acquired brain injury. However, a number of steps must be taken before the findings can be translated from animal models to human studies. First, the specific mechanisms of the neuroprotective or antiepileptogenic actions of the compounds need to be fully understood. In the Jvoti et al. study, correlative data suggested that antioxidant properties of curcumin, such as its effects on lipid peroxidation and protein oxidation, might account for a neuroprotective effect, but multiple other mechanisms could also be involved. One intriguing possibility arises from the recent finding that curcumin is an inhibitor of the mammalian target of rapamycin (mTOR) pathway, which has been implicated in mediating epileptogenesis in other models of epilepsy (10). Identification of the specific mechanisms will be helpful in optimizing treatments, leading to targeted therapies that are more effective than those currently available for brain injury and

providing information on adverse effects. Second, the pharmacokinetics of these compounds need to be elaborated and optimized for humans. For example, although the biological actions of a low-dose regimen of curcumin in the Jvoti et al. study was comparable to that documented in other studies, substantially higher doses were required to see a maximal effect on epileptogenesis. Furthermore, while water insoluble curcumin readily permeates the blood–brain barrier, it has notoriously poor gastrointestinal tract absorption. Third, the critical therapeutic window for optimal application following brain injury remains to be defined. Most importantly, as promising drug effects in animal models frequently have not been reproduced in clinical trials, controlled data on the efficacy and safety of resveratrol and curcumin in humans are needed. Although the idea of natural, dietary therapies is inherently attractive to many people, time will tell whether herbal remedies have an established place in epilepsy therapy.

by Michael Wong, MD, PhD

## References

1. Kwan P, Brodie MJ. Refractory epilepsy: mechanisms and solutions. *Expert Rev Neurother* 2006;6:397–406.
2. Temkin NR. Antiepileptogenesis and seizure prevention trials with antiepileptic drugs: Meta-analysis of controlled trials. *Epilepsia* 2001;42:515–524.
3. Loscher W, Schmidt D. New horizons in the development of antiepileptic drugs: Innovative strategies. *Epilepsy Res* 2006;69:183–272.
4. Schachter SC. Botanicals and herbs: A traditional approach to treating epilepsy. *Neurotherapeutics* 2009;6:415–420.
5. Saiko P, Szakmary A, Jaeger W, Szekeres T. Resveratrol and its analogs: Defense against cancer, coronary disease and neurodegenerative maladies or just a fad? *Mutation Res* 2008;658:68–94.
6. Gupta YK, Briyal S, Chaudhary G. Protective effect of trans-resveratrol against kainic acid-induced seizures and oxidative stress in rats. *Pharmacol Biochem Behav* 2002;71:245–249.
7. Wang Q, Yu S, Simoni A, Rottinghaus G, Sun GY, Sun AY. Resveratrol protects against neurotoxicity induced by kainic acid. *Neurochem Res* 2004;29:2105–2112.
8. Hatcher H, Planalp R, Cho J, Torti FM, Torti SV. Curcumin: From ancient medicine to current clinical trials. *Cell Mol Life Sci* 2008;1631–1652.
9. Sumanont Y, Murakami Y, Tohda M, Vajragupta O, Watanabe H, Matsumoto K. Effects of manganese complexes of curcumin and diacetylcurcumin on kainic acid-induced neurotoxic responses in the rat hippocampus. *Biol Pharm Bull* 2007;30:1732–1739.
10. Beevers CS, Li F, Liu L, Huang S. Curcumin disrupts the mammalian target of rapamycin-raptor complex. *Cancer Res* 2009;69:1000–1008.